REMARKS

Claims 154, 166, 176, 186, 195, 247 and 258 have been canceled. Claims 151, 163, 175, 185, 194, 198, 204, 213, 217, 246, 257, 292, 296 and 355 have been amended. Claims 151-153, 155-165, 167-175, 177-185, 187-194, 196-220, 246, 248-257, 259-266, 292-356 are pending.

Claims 151, 163, 175, 185, 194, 204, 213, 217, 246, 257, 292 and 296 have been amended to recite that the antibody or antigen-binding fragment inhibits binding of a ligand to said C-C chemokine receptor 3 protein. Support is found, for example, at page 35, line 30 through page 36, line 3.

Claims 198 and 355 have been amended to correct informalities.

This Amendment adds no new matter.

REJECTIONS UNDER 35 U.S.C. § 102

I. WO 94/111504 (Horuk *et al.*)

Claims 151-158, 160-166, 168-170, 172-176, 178-180, 182-189, 191-195, 197-199, 201-208, 210-220, 246-257, 253-261, 263-266, 292-299, 308-310, 313-315, 317-322, 325-327, 329-336, 338-343, 345-347 and 349-356 are rejected under 35 U.S.C. § 102(a) as being anticipated by WO 94/111504 (Horuk *et al.*). The Examiner states that Horuk *et al.* teaches polyclonal antibodies that bind CKR-1 and antibodies that antagonize CKR-1 activity or binding. The Examiner refers to Sequence Comparison A and Sequence Comparison B which are said to be attached to the Office Action. It appears that the Examiner intended to refer to Sequence Comparison A and Sequence Comparison B that were provided with the Office Action dated October 8, 2002 (Paper 27). Those sequence comparisons show that a region of 41 amino acids, that includes the "DRYLAI" motif, is found in the amino acid sequence of CKR-1, SEQ ID NO:4 and SEQ ID NO:6. The Examiner concludes that anti-CKR-1 antibodies would inherently compete for binding to SEQ ID NO:4 or SEQ ID NO:6 because the antibodies would be competing for the same binding site. The Examiner further states that the polynucleotide which encodes CKR-1 would hybridize to SEQ ID NO:3 or SEQ ID NO:5 under the conditions recited in the claims, and that CKR-1 binds RANTES and other C-C chemokine ligands.

Claims 246-257 and Claims 253-261 are included in the rejection. It appears that the Examiner may have intended to indicate that Claims 246-257 and 258-261 are subject to the rejection. Clarification is requested for the record.

With regard to the 41 amino acid region of sequence identity that the Examiner identified in Sequence Comparison A and Sequence Comparison B, the Examiner's attention is directed to the annotated copies of FIGS. 1A-1C of Horuk *et al.* provided herewith (Exhibit). The 41 amino acid region identified by the Examiner is highlighted and underlined on the copies, which clearly show that this sequence is part of transmembrane spanning domains 3 and 4 and the intracellular loop connecting these domains. Amino acid sequences that are within the transmembrane or intracellular domains of a chemokine receptor are not available for antibody (or antigen-binding fragment thereof) binding when the chemokine receptor is expressed on the surface of a cell, and antibodies (or antigen-binding fragments thereof) that have binding specificity for such regions would not inhibit binding of ligand to a C-C chemokine receptor 3 protein. Any antibodies that might bind this 41 amino acid region would not inherently bind the extracellular portions of CKR1 or C-C chemokine receptor 3, and would not inhibit binding of a ligand to the receptor because ligand binding is a function associated with the extracellular domains of receptors. In addition, any antibodies that might bind the shared 41 amino acid region would not bind a receptor that is expressed on the surface of a cell because transmembrane spanning domains 3 and 4 and the intracellular loop connecting these domains would not be accessible for antibody binding.

Independent Claims 151, 163, 175, 185, 194, 204, 213, 217, 246, 257, 292 and 296 have been amended to recite that the antibody or antigen-binding fragment "inhibits binding of a ligand to said C-C chemokine receptor 3 protein." These claims do not read on an antibody that fortuitously binds the 41 amino acid region that the Examiner identified as being shared by CKR-1, SEQ ID NO: 4 and SEQ ID NO:6. Therefore, Claims 151-153, 155-158, 160-165, 168-170, 172-175, 178-180, 182-189, 191-194, 197-199, 201-208, 210-220, 246, 248-257, 259-261, 263-266 and 292-299 are not anticipated.

Similarly, independent Claims 308, 320, 332, 341 and 353-356 recite that the antibody or antigen-binding fragment has binding specificity for a C-C chemokine receptor 3 protein that is expressed on the surface of a cell. These claims do not read on an antibody that fortuitously binds the 41 amino acid region that the Examiner identified as being shared by CKR-1, SEQ ID NO: 4 and SEQ ID NO:6. Therefore, Claims 308-310, 313-315, 317-322, 325-327, 329-336, 338-343, 345-347 and 349-356 are not anticipated.

II. U.S. Patent No. 5,707,815 (Charo *et al.*).

Claims 167, 175-177, 179, 180, 182-184, 187-189, 194-196, 206-208, 213-216, 246-248, 250, 251, 253-261, 292-295, 308-312, 314, 315, 317-324, 326, 327, 329-336, 338-344, 346, 347, 349-353 and 355 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,707,815 (Charo *et al.*). The Examiner states that Charo *et al.* discloses antibodies that bind the MCP-1RA and MCP-1RB receptors at column 16, lines 15-18. The Examiner refers to Sequence Comparison C which is said to be attached to the Office Action. It appears that the Examiner intended to refer to Sequence Comparison C that was provided with the Office Action dated October 8, 2002 (Paper 27). Sequence Comparison C shows that a region of 22 amino acids, that includes the "DRYLAI" motif, is found in the amino acid sequence of SEQ ID NO:13 of Charo *et al.* and Applicants' SEQ ID NO:2. The Examiner concludes that antibodies that bind MCP-1RA or MCP-1RB would also bind SEQ ID NO:2. The Examiner further states that the polynucleotide which encodes MCP-1RA or MCP-1RB would hybridize to SEQ ID NO:3 under the conditions recited in the claims.

With regard to the 22 amino acid region of sequence identity that the Examiner identified in Sequence Comparison C, the Examiner's attention is directed to column 21, lines 44-48 of Charo *et al.* which teach, "[a] striking identity between the MCP-1A receptor and the MIP-1α/RANTES receptor is found in the sequence IFFIILLTI DRYLAIV HAVFAL(K/R) ARTVTFGV (SEQ ID NOS: 13 and 14), which occurs at the end of the third transmembrane domain." (Charo *et al.* at column 21, lines 44-48; Emphasis added.) This teaching reveals that the region of 22 amino acids from SEQ ID NO:13 of Charo *et al.* identified in Sequence Comparison C is part of the third transmembrane domain of MCP-1RA and MCP-1RB.

Therefore, any antibodies that might bind the 22 amino acid region would not inherently bind the extracellular portions of MCP-1RA, MCP-1RB or C-C chemokine receptor 3 and would not inhibit binding of a ligand to the receptor. In addition, any antibodies that might bind the shared 22 amino acid region would not bind a receptor that is expressed on the surface of a cell because the third transmembrane domain would not be accessible for antibody binding.

Independent Claims 163, 175, 185, 194, 204, 213, 246, 257 and 292 have been amended to recite that the antibody or antigen-binding fragment "inhibits binding of a ligand to said C-C chemokine receptor 3 protein." These claims do not read on an antibody that fortuitously binds the 22 amino acid region that the Examiner identified as being shared by MCP-1RA, MCP-1RB and SEQ ID NO:2. Therefore, Claims 167, 175-177, 179, 180, 182-184, 187-189, 194, 196, 206-208, 213-216, 246, 248, 250, 251, 253-257, 259-261, 292-295 are not anticipated.

Similarly, independent Claims 308, 320, 332, 341, 353 and 355 recite that the antibody or antigen-binding fragment has binding specificity for a C-C chemokine receptor 3 protein that is expressed on the surface of a cell. These claims do not read on an antibody that fortuitously binds the 22 amino acid region that the Examiner identified as being shared by MCP-R1A, MCP-R1B and SEQ ID NO:2. Therefore, Claims 308-312, 314, 315, 317-324, 326, 327, 329-336, 338-344, 346, 347, 349-353 and 355 are not anticipated.

Reconsideration and withdrawal of the rejections under 35 U.S.C. § 102 are requested.

REJECTIONS UNDER 35 U.S.C. § 103

I. WO 94/1154 (Horuk *et al.*) in view of U.S. Patent No. 5,530,101 (Queen *et al.*)

Claims 151-154, 156-166, 168-176, 178-195, 197-224, 226-247, 249-270, 272-299 and 303-307 and Claims 308-310 and 313-356 are rejected under 35 U.S.C. § 103(a) as being obvious over WO 94/1154 (Horuk *et al.*) in view of U.S. Patent No. 5,530,101 (Queen *et al.*). The Examiner refers to Sequence Comparison A and Sequence Comparison B which show that the CKR-1 disclosed by Horuk *et al.* contains a 41 amino acid region that is also found in SEQ

ID NO:4 and SEQ ID NO:6. Based upon this region of amino acid sequence identity, the Examiner concludes that the antibodies disclosed by Horuk *et al.* would bind SEQ ID NO:4 or SEQ ID NO:6, and that they would compete with other antibodies for binding to SEQ ID NO:4 or SEQ ID NO:6, because they would be competing for the same binding site. (Office Action at page 5, lines 16 through 21.) In maintaining the rejection, the Examiner states that the claims do not recite that the claimed antibody is targeted to polypeptides of SEQ ID NO:2 or 4 when they are expressed on the cell surface. (Office Action at page 6, lines 19-21.) The Examiner further states that antibodies disclosed in Horuk *et al.* would be expected to bind the polypeptides of SEQ ID NO:4 or 6 if the polypeptides were isolated from the cell membrane. (Office Action at sentence bridging pages 6 and 7.)

Claims 221-224, 226-245, 267-270 and 272-291, which are included in the statement of rejection, were previously cancelled.

Claims 303-307 are also included in the statement of rejection but are indicated as being allowed in the Office Action Summary and as being allowable in the Conclusion on page 9 of the Office Action. Clarification of the status of Claims 303-307 is requested.

Independent Claims 151, 163, 175, 185, 194, 204, 213, 217, 246, 257, 292 and 296 have been amended to recite that the antibody or antigen-binding fragment "inhibits binding of a ligand to said C-C chemokine receptor 3 protein." The subject matter of these claims is not obvious, because no references of record (alone or in any combination) suggest antibodies or antigen-binding fragments thereof that have binding specificity for a C-C chemokine receptor 3 protein and inhibit binding of a ligand to the receptor, or provide a reasonable expectation of success in producing such an antibody or antigen-binding fragment. Additionally, there is no scientific basis to conclude that an antibody or antigen-binding fragment that binds an epitope in a transmembrane or intracellular domain of CKR-1 would bind a C-C chemokine receptor 3 protein and inhibit ligand binding, because ligand binding is a function associated with the extracellular domains of receptors. Therefore, the subject matter of Claims 151-153, 156-165, 168-175, 178-185, 187-194, 197-220, 246, 249-257, 259-266 and 292-299 is not obvious.

Contrary to the Examiner's statement (Office Action, at page 6, lines 19-21), independent Claims 308, 320, 332, 341 and 353-356 recite that the antibody or antigen-binding fragment has binding specificity for a C-C chemokine receptor 3 protein that is expressed on the surface of a cell. The subject matter of these claims is not obvious, because no references of record (alone or in any combination) suggest antibodies or antigen-binding fragments thereof that have binding specificity for a C-C chemokine receptor 3 protein that is expressed on the surface of a cell, or provide a reasonable expectation of success in producing such an antibody or antigen-binding fragment. Amino acid sequences that are within the transmembrane or intracellular domains of a chemokine receptor are not available for antibody (or antigen-binding fragment thereof) binding when the chemokine receptor is expressed on the surface of a cell, and antibodies (or antigen-binding fragments thereof) that have binding specificity for such regions would not bind to a C-C chemokine receptor 3 protein that is expressed on the surface of a cell. Additionally, there is no scientific basis to conclude that an antibody or antigen-binding fragment that binds an epitope in a transmembrane or intracellular domain of a chemokine receptor would bind a C-C chemokine receptor 3 protein that is expressed on the surface of a cell. Therefore, the subject matter of Claims 308-310 and 313-356 is not obvious, because no references of record (alone or in any combination) suggest antibodies or antigen-binding fragments thereof that have binding specificity for a C-C chemokine receptor 3 protein that is expressed on the surface of a cell, or provide a reasonable expectation of success in producing such an antibody or antigen-binding fragment.

II. U.S. Patent No. 5,707,815 (Charo *et al.*) in view of U.S. Patent No. 5,530,101 (Queen *et al.*)

Claims 151, 155, 157-162, 167, 175-177, 179-184, 194-196, 198-203, 212-216, 221-225, 228-233, 238-241, 246-248, 250-256, 259-262, 267-271, 273-279, 284-287, 292-295 and 303-307 and Claims 308-312, 314-324 and 332-356 are rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,707,815 (Charo *et al.*) in view of U.S. Patent No. 5,530,101 (Queen *et al.*). The Examiner refers to Sequence Comparison C which shows that MCP-1RA and MCP-1RB disclosed by Charo *et al.* contain a 22 amino acid region that is also found in SEQ ID NO:2. Based upon this region of amino acid sequence identity, the Examiner concludes that the

antibodies disclosed by Charo *et al.* would bind SEQ ID NO:2. (Office Action at page 7, lines 14-16.) In maintaining the rejection, the Examiner states that the claims do not recite that the claimed antibody is targeted to polypeptides of SEQ ID NO:2 or 4 when they are expressed on the cell surface. (Office Action at page 8, lines 16-18.) The Examiner further states that antibodies directed to CCR1 and CCR2 would be expected to bind the polypeptides of SEQ ID NO:2 if the polypeptides were isolated from the cell membrane. (Office Action, sentence bridging pages 6 and 7.)

Claims 221-225, 228-233, 238-241, 245-246, 267-271, 273-279 and 284-287, which are included in the statement of rejection, were previously cancelled.

Claims 303-307 are also included in the statement of rejection, but are indicated as being allowed in the Office Action Summary and as being allowable in the Conclusion on page 9 of the Office Action. Clarification of the status of Claims 303-307 is requested.

Independent Claims 151, 163, 175, 194, 204, 213, 217, 246, 257, 292 and 296 have been amended to recite that the antibody or antigen-binding fragment "inhibits binding of a ligand to said C-C chemokine receptor 3 protein." The subject matter of these claims is not obvious, because no references of record (alone or in any combination) suggest antibodies or antigen-binding fragments thereof that have binding specificity for a C-C chemokine receptor 3 protein and inhibit binding of a ligand to the receptor, or provide a reasonable expectation of success in producing such an antibody or antigen-binding fragment. Additionally, there is no scientific basis to conclude that an antibody or antigen-binding fragment that binds an epitope in a transmembrane or intracellular domain of a chemokine receptor would bind a C-C chemokine receptor 3 protein and inhibit ligand binding, because ligand binding is a function associated with the extracellular domains of receptors. Therefore, the subject matter of Claims 151, 155, 157-162, 167, 175, 177, 179-184, 194, 196, 198-203, 212-216, 246, 248, 250-256, 259-262 and 292-295 is not obvious.

Contrary to the Examiner's statement (Office Action, at page 8, lines 16-18), independent Claims 308, 320, 332, 341 and 353-356 recite that the antibody or antigen-binding fragment has

binding specificity for a C-C chemokine receptor 3 protein that is expressed on the surface of a cell. The subject matter of these claims is not obvious because no references of record (alone or in any combination) suggest antibodies or antigen-binding fragments thereof that have binding specificity for a C-C chemokine receptor 3 protein that is expressed on the surface of a cell, or provide a reasonable expectation of success in producing such an antibody or antigen-binding fragment. Amino acid sequences that are within the transmembrane or intracellular domains of a chemokine receptor are not available for antibody (or antigen-binding fragment thereof) binding when the chemokine receptor is expressed on the surface of a cell, and antibodies (or antigen-binding fragment thereof) that have binding specificity for such regions would not bind to a C-C chemokine receptor 3 protein that is expressed on the surface of a cell. Additionally, there is no scientific basis to conclude that an antibody or antigen-binding fragment that binds an epitope in a transmembrane or intracellular domain of a chemokine receptor would bind a C-C chemokine receptor 3 protein that is expressed on the surface of a cell. Therefore, the subject matter of Claims 308-312, 314-324 and 332-356 is not obvious, because no references of record (alone or in any combination) suggest antibodies or antigen-binding fragments thereof that have binding specificity for a C-C chemokine receptor 3 protein that is expressed on the surface of a cell, or provide a reasonable expectation of success in producing such an antibody or antigen-binding fragment.

Reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 are requested.

Information Disclosure Statement

Supplemental Information Disclosure Statements (SIDS) were filed on April 11, 2003 and May 21, 2003. Acknowledgment of consideration of the information provided in the SIDS is requested in the next Office Communication.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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